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Clinicopathologic Characteristics of Young Gastric Cancer Patients: Diagnostic Staging Accuracy and Survival

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Purpose: The purpose of this study was to investigate the clinicopathologic characteristics of young gastric cancer patients and analyze the risk factors for stage underestimation and survival.

Methods: Relevant data of 5029 patients who underwent surgery for gastric cancer at Seoul National University Bundang Hospital between 2003 to 2014 were collected. Patients were divided based on age (younger group and older group). Clinical stages were compared to pathologic stages for accuracy, and risk factors for underestimation were analyzed using univariate and multivariate analysis regression. Overall survival and cancer-specific survival were analyzed using the Kaplan-Meier method.

Results: A total of 4396 patients were eligible for inclusion. The younger group was an independent risk factor for nodal metastasis (RR=1.44, 95% CI 1.06~1.95) and an independent risk factor for clinical N-stage underestimation (RR=1.50, 95% CI=1.14~1.98). However, there was no significant difference in 5-year cancer-specific survival for both age groups (92.2% vs 90.2%, p=0.306).

Conclusion: In conclusion, intra-operative investigation of T-stage with standard operation should be done in young gastric cancer patients as they have a higher incidence of lymph node metastasis, with greater frequency of stage underestimation.

Keywords: Stomach neoplasm, Diagnosis, Survival, Age groups, Surgery

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INTRODUCTION

Gastric cancer is the 5th most common cancer and 3rd most common cause of cancer-related deaths worldwide,[1] with incidence rates highly concentrated in East Asia and Latin America.[1,2] Recent advances in surgical and endoscopic diagnostic techniques have progressively improved patient outcomes, becoming vitally important for establishing accurate clinical staging and determining suitable treatment strategies.

There are multiple challenges in making accurate clinical diagnosis for gastric cancer; one of which is accurately examining the lymph node metastasis. Based on previous studies, diffuse type cancers have more lymph node metastasis compared with its counterparts,[3] and they are often inaccurately diagnosed.[4,5] Underestimation of lymph node metastasis at the pre-operative stage may pose as an obstacle in deciding the correct range of lymph node dissection. Since young patients are known to have higher frequencies of undifferentiated and diffuse tumor

types,[6-8] it is even more challenging to appropriately determine treatment strategies.

Hence, the purpose of this study was twofold: (1) to investigate the accuracy of clinical staging based on two – younger and older – age groups; and (2) to evaluate whether the underestimation of pre-operative clinical staging is more prevalent in the younger population than in the older population. We hypothesized that it would be more prevalent in the younger population compared with the older population, and thus, influencing survival.

MATERIALS AND METHODS

Patients

A total of 5029 patients who underwent radical gastrectomy for gastric cancer between May 1st 2003 and December 31st 2014 at Seoul National University Bundang Hospital were initially screened. Patients who underwent non-curative surgery (381), non-radical gastrectomy (183) without pathologic data (59), or with multiple gastric cancers (10) were excluded from this study because they may hinder a clear evaluation of the surgical outcomes. A total of 4396 patients were eligible for investigation. This study was approved by the Institutional Review Board and was performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of this study, as data were de-identified prior to analysis.

Data collection and definition of variables

This study retrospectively analyzed the patient records for name, patient number, stage, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status class, tumor location (esophagogastric junction, proximal, middle, distal), average tumor size, Lauren histologic classification (intestinal, diffuse, mixed), operation name, operation time, estimated blood loss (EBL), clinical stage, pathologic stage, and survival. Tumors were staged according to the American Joint Committee on Cancer (AJCC), 8th edition. Clinical staging was evaluated using the pre-operative computed tomography (CT) and endoscopic ultrasonography (EUS) from the patient medical records. Clinical stage was considered conservatively; higher stage of the two exams were selected. Patients without EUS results and no visualization of the main tumor in CT were designated as T1. Accuracy, overestimation, and underestimation of clinical staging was determined by comparing the clinical staging to the pathologic staging. Identical pathologic stage was designated as accurate; lower pathologic staging was designated as overestimation; and higher pathologic staging was designated as underestimation.

Patients' death information was obtained from the microdata integrated service database of the Korea Statistics Promotion Institute. Recurrence data was collected through reviewing the medical record for follow-up CT scans, esophagoduodenoscopy (EGD), or ultrasonography. Abdominal ultrasonography and computed tomography (CT) were checked every 6 months in the case of early gastric cancer patients, and abdomen-pelvis CT scan was evaluated least every 6 months in advanced cancer patients. The survival and recurrence statuses were determined in March 2020.

According to recently nationwide statistics in Korea, there is a demographic differences for age below 40,[9] and clinicopathologic features analyzed in this study tended to be different between patients aged 40 years or less and those aged 40 years or over. Thus, we divided our study population into two groups based on age cut-off of 40 years of age. This is similar to cut-off age used in previous studies.[7,10,11]

Statistical analysis

Categorical data were compared using Pearson's Chi-squared test, and continuous data were compared using the independent t test. Categorical variables were presented as numbers with percentages, and continuous data were expressed as the mean ± standard deviation. Survival was examined using the Kaplan Meier method. A p value of less than 0.05 was considered to be statistically significant. Data analysis was done using the SPSS program, version 22 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

All patients underwent R0 resection of tumor with radical lymph node dissection. The median follow-up was 52.2 months after surgery. Demographics of the younger group (YG) and the older group (OG) are outlined in Table 1. Female was notably more prominent in the younger group compared with the older group. There was no significant difference in the number patients within each pathologi T-staging between the two groups; both groups showed a higher proportion of the T1 stage (62.6% in YG vs. 60.2 in OG). Similar trend was found for the pathologic N-stage, where N0 had the highest proportion in both groups. The younger group had a higher incidence of lymph node invasion compared with the older group (41.2% vs. 34.9%). TNM stage was similar in both groups, with no significant statistical difference. A higher proportion of diffuse or mixed type cancers was seen in the younger group than in the older group (86.6% vs. 44.2). As expected, the younger group had a significantly lower ASA class than the older group; however, the mean BMI was similar

Table 1. Patient characteristics

	Young (N=337, %)	Old (N=4059, %)
Age	35.99 (20~40)	61.98 (41~92)
Gender (%)		
M	156 (46.3)	2792 (68.8)
F	181 (53.7)	1267 (31.2)
Location (%)		
GE Junction	5 (1.5)	85 (2.1)
Proximal	59 (17.5)	679 (16.7)
Middle	123 (36.5)	943 (23.2)
Distal	137 (40.7)	2269 (55.9)
Diffuse	13 (3.9)	83 (2.0)
Average tumor size (cm)	3.918 (0.4~19.0)	3.891 (0.1~21.0)
Clinical stage (%)		
T1	185 (54.9)	2064 (50.8)
T2	77 (22.8)	845 (20.8)
T3	56 (16.6)	819 (20.2)
T4	19 (5.6)	331 (8.2)
N0	264 (78.3)	3036 (74.8)
N1	64 (19.0)	820 (20.2)
N2	6 (1.8)	159 (3.9)
N3	3 (0.9)	44 (1.1)
Pathologic stage (%)		
T1	211 (62.6)	2442 (60.2)
T2	25 (7.4)	499 (12.3)
T3	59 (17.5)	632 (15.6)
T4	42 (12.5)	486 (12.0)
N0	198 (58.8)	2649 (65.3)
N1	49 (14.5)	494 (12.3)
N2	54 (16.0)	370 (9.1)
N3	36 (10.7)	546 (13.5)
TNM		
Stage I	204 (60.5)	2616 (64.4)
Stage II	53 (15.7)	625 (15.4)
Stage III	80 (23.7)	818 (20.2)
Histology (%)		
Intestinal	45 (13.4)	2268 (55.9)
Diffuse	274 (81.3)	1590 (39.2)
Mixed	18 (5.3)	201 (5.0)
BMI (kg/m^2)	22.54 (14.43~34.60)	23.67 (14.01~37.26)

Table 1. Continued

	Young (N=337, %)	Old (N=4059, %)
ASA class (%)		
1	288 (85.5)	1902 (46.9)
2	47 (13.9)	1951 (48.1)
≥3	2 (0.6)	206 (5.0)
Operation approach (%)		
Laparoscopic	262 (77.7)	2886 (71.1)
Open	9 (2.7)	91 (2.2)
Open Conversion	66 (19.6)	1082 (26.7)
Type of operation (%)		
Distal gastrectomy	255 (75.7)	3181 (78.4)
Total gastrectomy	65 (19.3)	676 (16.7)
Proximal gastrectomy	13 (3.9)	175 (4.3)
Pylorus preserving gastrectomy	4 (1.2)	27 (0.7)
Lymph Node Dissection		
D1+	131 (38.9)	1523 (37.5)
≥D2	206 (61.1)	2536 (62.5)
Retrieved Lymph Nodes	51.84 (18~115)	51.19 (6~221)
Positive Lymph Nodes	2.70 (0~41)	2.89 (0~104)
Op Time (min)	183.33 (70~495)	185.18 (55~720)
EBL (mL)	102.97 (10~1200)	123.29 (10~6650)
Hospital stay (days)	6.93 (4~41)	8.43 (2~1432)

Table 2. Tendency of node metastasis for clinical and pathologic T stage

	Pathologic node negative	Pathological node positive	*p* value
Clinical early gastric cancer (cT1)			0.007
Younger group	146 (78.9)	39 (21.1)	
Older group	1780 (86.2)	284 (13.8)	
Clinical advanced gastric cancer (≥cT2)			0.025
Younger group	52 (34.2)	100 (65.8)	
Older group	869 (43.6)	1126 (56.4)	
Pathologic early gastric cancer (pT1)			0.011
Younger group	173 (82.0)	38 (18.0)	
Older group	2149 (88.0)	293 (12.0)	
Pathologic advanced gastric cancer (≥pT2)			0.001
Younger group	25 (19.8)	101 (80.2)	
Older group	500 (30.9)	1117 (69.1)	

in both groups. Both the younger group and the older group had similar operations, with most patients receiving the laparoscopic approach. The younger group had more laparoscopic approaches than the older group (77.7% vs. 71.1%), and lower open conversion surgeries (19.6% vs. 26.7%). Most patients underwent distal gastrectomy (75.7% vs. 78.4%), followed by total gastrectomy (19.3%

vs. 16.7), and function preserving gastrectomy (1.2% vs. 0.7%). The majority of patients in both groups underwent D2 lymph node dissection (61.1% vs 62.5%), with a similar average of number of retrieved lymph nodes (51.84 vs 51.19) and positive lymph nodes (2.70 vs 2.89). Both groups had comparable operation time and estimated blood loss.

Node metastasis according to T-stages

Node metastasis was more frequently observed in the younger group than in the older group for clinical early gastric cancer (EGC) (21.1% in YG vs. 13.8% in OG, p=0.007) as well as pathologic EGC (18.0% vs 12.0%, p=0.011) (Table 2). Furthermore, similar results were seen in both clinical advanced gastric cancer (AGC) (65.8% vs 56.4% p=0.025) and pathologic AGC (80.2% vs 69.1% p=0.001). The younger group was an independent risk factor for nodal metastasis (RR=1.44, 95% CI 1.06~1.95), as with large tumor size (RR=2.94, 95% CI 2.22~3.89) and higher T-stage and diffuse or mixed type histology (RR=1.25, 95% CI 1.06~1.49) (Table 3).

Accuracy of preoperative staging

Clinical T-stage accuracy in terms of histologic types showed that there was a difference of accuracy, underestimation and overestimation rates between diffuse and mixed types compared with the intestinal type (p=0.033) (Table 4). And underestimation rate was higher for the diffuse and mix types compared with the intestinal type (23.2% vs 10.3%). Similarly, accuracy, underestimation and overestimation rates showed difference comparing the different age groups (p<0.001) with underestimation rates higher for the younger group compared with the older group (20.5% vs 16.1%). This trend continued when comparing between the

Table 3. Risk factors for lymph node metastasis

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age						
≥40 years	Reference					
<40 years	1.32	1.05~1.65	0.017	1.4	1.03~1.89	0.031
Gender						
Male	Reference					
Female	1.15	1.01~1.31	0.033	1.15	0.97~1.37	0.867
Tumor size						
<2 cm	Reference					
≥2 cm	10.19	7.89~13.18	<0.001	3.01	2.28~3.99	<0.001
pT-stage						
T1	Reference					
T2	6.02	4.90~7.40	<0.001	4.99	4.02~6.18	<0.001
T3	17.59	14.38~21.52	<0.001	13.42	10.85~16.61	<0.001
T4	73.51	53.18~101.60	<0.001	50.84	36.3~71.22	<0.001
Tumor location						
Distal	Reference					
Middle	1.14	0.98~1.34	0.087	0.79	0.65~0.97	0.024
Upper	1.91	1.62~2.24	<0.001	0.88	0.71~1.10	0.263
Diffuse	22.15	11.09~44.24	<0.001	2.01	0.90~4.47	0.089
Histology						
Intestinal	Reference					
Diffuse & mixed	2.06	1.81~2.33	<0.001	1.25	1.06~1.49	0.010

Table 4. Accuracy of clinical staging

	Accurate	Underestimated	Overestimated	*p* value
T-stage				
Younger Group	211 (62.6)	69 (20.5)	57 (16.9)	0.033
Older Group	2530 (62.3)	653 (16.1)	876 (21.6)	
Intestinal type	1524 (65.9)	238 (10.3)	551 (23.8)	<0.001
Diffuse and mixed type	1217 (58.4)	484 (23.2)	382 (18.3)	
N-Stage				
Younger Group	223 (66.2)	90 (26.7)	24 (7.1)	<0.001
Older Group	3014 (74.3)	716 (17.6)	329 (8.1)	
Intestinal type	1802 (77.9)	322 (13.9)	189 (8.2)	<0.001
Diffuse and mixed type	1435 (69.0)	484 (23.2)	164 (7.9)	

Table 5. Risk factors for underestimation of T-staging

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age						
≥40 years	Reference					
<40 years	1.34	1.02~1.77	0.037	0.89	0.66~1.20	0.441
Gender						
Male	Reference					
Female	1.27	1.07~1.49	0.005	1.05	0.88~1.26	0.564
Tumor size						
<2 cm	Reference					
≥2 cm	7.87		<0.001	6.27	4.30~9.13	<0.001
Tumor location						
Distal	Reference					
Middle	2.09	1.71~2.54	<0.001	1.71	1.40~2.10	<0.001
Upper	2.47	2.01~3.03	<0.001	2.04	1.65~2.52	<0.001
Diffuse	7.78	5.11~11.85	<0.001	4.36	2.84~6.70	<0.001
Histology						
Intestinal	Reference					
Diffuse and mixed	2.68	2.26~3.18	<0.001	2.05	1.71~2.46	<0.001

younger and older groups for the diagnostic accuracy of clinical N-staging.

In observing similar trends for a higher underestimation rate in the clinical staging for both diffuse type tumor and the younger group, we had conducted a subgroup analysis to see whether age played a role in making a difference in diagnostic accuracy rates (Supplementary Table 1). Both groups had no different accuracy rates for clinical T-stage when analyzed separately under each histologic type. Contrastingly, when analyzing the clinical N-stage accuracy for diffuse and mixed types of tumor, the younger group showed difference in diagnostic accuracy compared with the older group.

Risks of clinical stage underestimation

Table 5 illustrates the risk factors for clinical T-stage under-

estimation. In a multivariable analysis, tumor size greater than 2 cm was shown to have a higher relative risk (RR=6.27, 95% CI=4.30~9.13) compared with those less than 2 cm in size. Notably, tumors located in the upper portions of the stomach were shown to have a higher risk of underestimation than those located in the distal portions of the stomach. As expected, diffuse

Table 6. Risk factors for underestimation of N-staging

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age						
≥40 years	Reference					
<40 years	1.7	1.32~2.19	<0.001	1.5	1.14~1.98	0.004
Gender						
Male	Reference					
Female	1.37	1.17~1.61	<0.001	1.27	1.07~1.51	0.006
Tumor size						
<2 cm	Reference					
≥2 cm	4.95	3.70~6.62	<0.001	2.77	2.04~3.77	<0.001
pT-stage						
T1	Reference					
T2	3.7	2.96~4.63	<0.001	3.11	2.46~3.93	<0.001
T3	3.6	2.93~4.42	<0.001	2.82	2.26~3.51	<0.001
T4	4.14	3.32~5.17	<0.001	3.02	2.37~3.86	<0.001
Tumor location						
Distal	Reference					
Middle	1.26	1.04~1.51	0.016	1	0.82~1.22	0.981
Upper	1.25	1.02~1.53	0.03	0.84	0.68~1.05	0.118
Diffuse	2.65	1.72~4.09	<0.001	1	0.63~1.59	0.994
Histology						
Intestinal	Reference					
Diffuse & Mixed	1.87	1.60~2.19	<0.001	1.36	1.14~1.62	<0.001

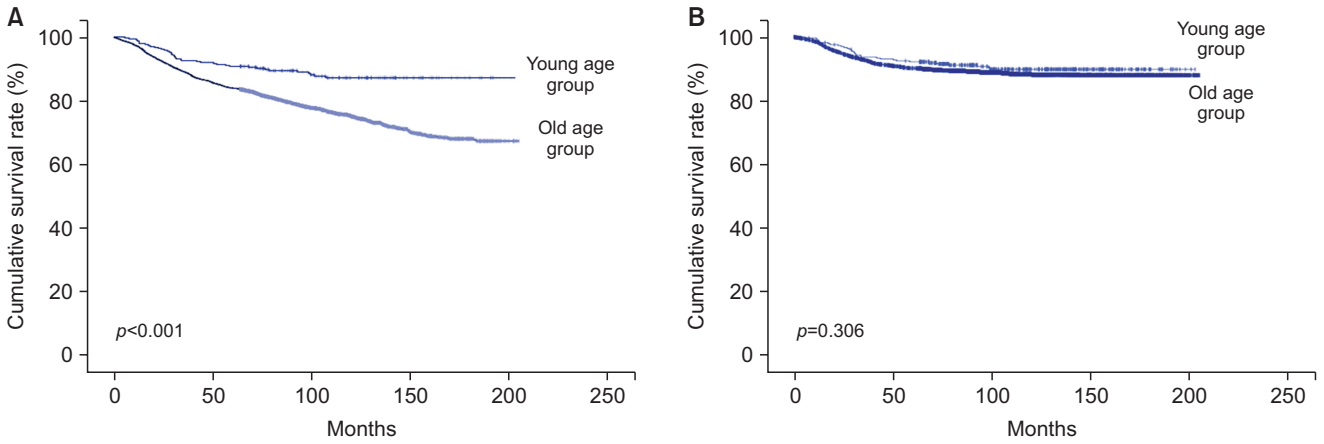

Fig. 1. Survival curves for age groups. (A) Overall survival. (B) Cancer-specific survival.

and mixed tumor types were shown to have a higher risk of underestimation compared with the intestinal tumor type (RR=2.05, 95% CI=1.71~2.46).

In contrast to the risks of clinical T-stage underestimation, multivariable analysis revealed a higher risk of clinical N-stage underestimation in both younger age (RR=1.50, 95% CI=1.14~1.98) and female gender (RR=1.27, 95% CI=1.07~1.51) (Table 6). Larger tumor size and higher pathologic T-stage also showed a higher risk of nodal stage underestimation. As anticipated, diffuse and mixed tumor types were likely to have a higher risk of nodal underestimation (RR=1.36, 95% CI=1.14~1.62). unlike T-staging, location of tumor did not have an impact in nodal stage underestimation.

Overall survival and cancer specific survival

The median follow-up periods were 111.1 months for the younger group and 101.8 months for the older group. The overall 5-year survival for the older group was significantly lower than that for the younger group (90.8% vs 84.0%, $p<0.001$) (Fig. 1A). There was no significant difference in 5-year cancer-specific survival for both groups (92.2% vs 90.2%, $p=0.306$) (Fig. 1B). Recurrence pattern showed no difference in both age groups (Supplementary Table 2).

DISCUSSION

Similar to previous studies, a higher proportion of females and a higher proportion of diffuse cancer type were seen in the younger population.[12-14] It still remains unclear why females are more prevalent in the younger population with gastric cancer. Some studies have hypothesized that estrogen may have an impact in gastric cancer growth,[10,15,16] as estrogen receptors were found in some gastric cancer patients. Whether or not estrogen may stimulate cancer growth, its association with the diffuse cancer type is convincing.[17,18]

More laparoscopic surgeries are performed in younger patients. This is because older patients are likely to have past surgical histories or other comorbidities that may come as an obstacle in laparoscopic surgeries. That is also the reason why open conversion surgeries are also more frequent among older patients; laparoscopic approach performed in higher stages of gastric cancer may require longer duration of surgery, which may jeopardize post-operative recovery.

Previous studies have revealed that undifferentiated carcinoma is more prevalent in younger patients and that undifferentiated tumors usually grow vertically.[19] Furthermore, CT scans have an accuracy rate of 60~70%,[4,5,20] when it comes to the evaluation of pre-operative nodal staging with a risk of nodal metastasis based on tumor depth instead of histologic subtypes.[21] These may explain the underestimation of the T-stage and N-stage in the younger group. Therefore, a thorough intra-operative investigation for enlarged lymph nodes is warranted in younger patients.

Herein, similar to previous studies, the overall survival turned out to be better for the younger group.[12-14] However, there was no difference in cancer specific survival between the two group. Initially, we assumed that since underestimation of nodal metastasis was higher in the younger group, cancer specific survival would be worse for the younger group, since the scope of surgical dissection is usually determined by the pre-operative staging. Similar cancer specific survival may be attributable to the fact that we have performed more radical lymph node dissection than expected. As an example, in the younger group, the number of EGC patients with node metastasis was higher (the younger group, 18.0% vs the older group, 12.0%), but the number of patients who had D2 or higher lymph node dissection was lower (YG 47.9% vs 48.5%). Similar trend was also observed in AGC patients. Lymph node metastasis were seen in 80.2% of the younger group and 69.1% of the older group for AGC patients, with number of patients who had D2 or higher lymph node dissection were 83.4% for the younger group and 83.8% for the older group. Since more radical surgery was performed regardless of the pre-operative staging, the influence of lymph node dissection became a negligible factor.

In conclusion, intra-operative investigation of T-stage with standard operation should be done in young gastric cancer patients as they have a higher incidence of lymph node metastasis, with greater frequency of stage underestimation.

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CONFLICT OF INTEREST

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